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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 13 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id No.: 109701. Permethrin: Review of a series 81-6 dermal sensitization study (guinea pig maximization test) and a series 85-2 dermal penetration study.

TOX CHEM No.: 652BB
PC No.: 109701
Barcode No.: D201418
Submission No.: S462393

FROM: John Doherty 6/8/95
Acting Section Head
Section IV, Toxicology Branch I
Health Effects Division (7509C)

TO:[1] Virginia Deitrich/Paul Lewis
Product Manager #51
Special Review and Reregistration Division 7508W

THROUGH: Marion Copley, DVM, 6/8/95
Toxicology Branch I
Health Effects Division (7509C)

and

Karl Baetcke, Ph.D.
Chief, Toxicology Branch I
Health Effects Division 7509C 6/9/95

I. CONCLUSION

Sensitization study. The dermal sensitization study (MRID No.: 41831106) which followed the guinea pig maximization protocol was reviewed and determined to be ACCEPTABLE. Although the study presented was positive, a weight of the evidence consideration does not justify regarding permethrin as a potential chemical dermal sensitizer to humans. No additional dermal sensitization studies are required at this time.

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[1]CC: Goerge LaRocca, PM #13 Registration Division 7505C

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Dermal penetration study. The dermal penetration study with the permethrin 2EC formulation (MRID No.: 43169001) was reviewed and determined to be ACCEPTABLE. The resulting data are considered useful for selecting a dermal penetration factor for permethrin for exposures to the 2EC formulation and similar formulations. Refer to DER and comments below for the selection of dermal penetration factors. Additional dermal penetration studies may be required to support risk assessments for other permethrin formulations.

II. Action Requested

The Zeneca Ag Products Company has submitted a series 81-6 dermal sensitization study (guinea pig maximization test) with permethrin and a series 85-2 dermal penetration study with rats using a 2EC formulation. These studies are further identified in Part IV below. These studies were reviewed and copies of the DERs are attached. The following comments apply.

III. Toxicology Branch Comments.

A. Dermal Sensitization Study.

1. The guinea pig maximization test presented indicated that permethrin was positive in this study. This study type however utilizes intradermal administration of the test material together with Freund's adjuvant and is considered to have a high rate of false positives. A weight of the evidence approach to determining if permethrin should be regarded as a chemical sensitizer was assessed. The key findings are as follows.

-The HED "one liners" file references 24 series 81-6 dermal sensitization studies with permethrin or its formulations. Only one study with a formulation was determined to be indicative of being a sensitizer. The other studies, including two other maximization tests with guinea pigs and at least two tests with humans did not indicate that permethrin was a sensitizer. Case reports indicating sensitization reactions to permethrin do not support a conclusion that permethrin is a sensitizer in humans.

Thus, it is HED's conclusion based on available evidence that permethrin should not be regarded as a chemical sensitizer.

B. Dermal Penetration Study.

1. The study was determined to be ACCEPTABLE and to be useful for selecting the dermal penetration factor for the 2EC formulation and related formulations. For these formulations, the following scheme should be used for selecting dermal

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penetration factors for risk assessment: 011574

Exposures ≤ 0.32 mg/kg, 45%

Exposures > 0.32 mg/kg, 22%

This scheme is considered generally appropriate for all exposure time intervals.

Refer to Appendix I of the DER for a discussion on how this scheme was devised. Table 2 of the DER presents the dose and time relationships for the dermal penetration and adherence of permethrin and can be consulted for if under some specific circumstances other dermal penetration factors need to be derived.

2. The above scheme for selection of the dermal penetration factors can be used for other formulations when they are similar to the 2EC formulation on a case by case basis. Additional series 85-2 dermal penetration studies may be necessary for other formulations of permethrin that are not similar to the 2EC formulation.

IV. Studies Reviewed

Study Identification	Material	MRID No.:	Results	Classification
81-6. Dermal sensitization (guinea pig maximization test) ICI Central Toxicology Laboratory, Study No.: CTL/P/2456 Feb 21, 1989.	Technical permethrin Purity = 95.6% CTL reference number Y00040/085/001	410311-06	A group of 20 female guinea pigs (Dunkin Hartley) were inducted intradermally with 10% permethrin in corn oil and both neat and 30% solution of permethrin and later challenged with neat and 30% permethrin solutions in a guinea pig maximization test (MRID No.: 41031106). 9 of 20 total guinea pigs produced indications of a positive response when none of the 10 control pigs had definite scores for reaction. Permethrin was demonstrated to be a moderate dermal sensitizer in the guinea pig maximization test, but a weight of evidence evaluation of other sensitization study data do not indicate that permethrin should be regulated as a potential senstizer.	ACCEPTABLE

85-2. Dermal penetration-rats Zeneca Central Toxicology Laboratory, Study No.: CTL/P/3984, June 11, 1993	^{14}C labelled permethrin in 2EC formulation	431690-01	Four groups of 24 male rats (Wistar strain) were dosed dermally at 9.1, 0.86, 0.08 or 0.004 mg permethrin/rat applied in concentrated 2EC formulation or water diluted formulation and sacrificed at 0.5, 1, 2, 4, 10 and 24 hou. after application to assess for dermal penetration. (MRID No. 43169001). Total recovery ranged 95.86% ± 2.81% for the 9.1 [illegible] to 99.77% ± 3.53% for the 0.[illegible]mg group indicating good experimental efficiency. Systemically absorbed and the total of the systemically absorbed plus potentially absorbable (content of stratum corneum and residual skin) varied widely because permethrin adhered to the skin. The following percentages should be used the dermal penetration factors for risk assessment for the 2EC and closely related formulations of permethrin. Exposures ≤ 0.32 mg/kg, 45%. Exposures > 0.32 mg/kg, 22%. These percentages are generally appropriate for all time intervals.	ACCEPTABLE

Reviewed by: John Doherty, Ph.D., D.A.B.T.
Section IV, Toxicology Branch I (7509C)
Secondary reviewer: Marion Copley, DVM
Section IV, Toxicology Branch I (7509C)

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DATA EVALUATION REPORT

STUDY TYPE: 85-2. Dermal Penetration - rats.

MRID NO.: 431690-01 **TOX. CHEM. NO.:** 652BB
PC No.: 109701

TEST MATERIAL: Permethrin formulation 2EC, unlabelled and ^{14}C labelled permethrin. Refer to test material section below for additional details.

STUDY NUMBER: CTL/P/3984

SPONSOR: Zeneca Ag Products

TESTING FACILITY: Zeneca Central Toxicology Laboratory

TITLE OF REPORT: "Permethrin: In vivo Percutaneous Absorption Study in the Rat"

AUTHOR: R.E. Lythgoe

REPORT ISSUED: June 11, 1993
[October 1992 to February 1993]

EXECUTIVE SUMMARY:

Four groups of 24 male rats (Wistar strain) were dosed dermally at 9.1, 0.86, 0.08 or 0.004 mg ^{14}C permethrin/rat applied in concentrated 2EC formulation or water diluted formulation. The rats were sacrificed at 0.5, 1, 2, 4, 10 and 24 hours after application to assess for dermal penetration. MRID No.: 43169001.

Total recovery ranged from 95.86% ± 2.81% for the 9.1 mg group to 99.77% ± 3.53% for the 0.08 mg group indicating good experimental efficiency. Systemically absorbed and the total of the systemically absorbed plus potentially absorbable (content of stratum corneum and residual skin) varied widely because permethrin adhered to the skin. The following percentages should be used the dermal penetration factors for risk assessment with the 2EC and closely related formulations of permethrin.

Exposures ≤ 0.32 mg/kg, 45%.

Exposures > 0.32 mg/kg, 22%.

These percentages are generally appropriate for all time intervals.

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Classification: ACCEPTABLE. The study satisfies the requirement for a series 85-2 dermal penetration study for the 2EC formulation and similar formulations on a case by case basis. Additional series 85-2 dermal penetration data may be required to support registrations for formulations not similar to the 2EC formulation assessed in this study.

Quality Assurance Statement: Provided.
Good Laboratory Practice Statement: Provided.
Statement of Data Confidentiality Claim: Provided. No claim of confidentiality made.

REVIEW

Experimental Constants:

Test Chemicals:

Formulation:	Specially prepared formulation equivalent to 2EC 2lb/gal without permethrin

Unlabelled material:

Chemical:	Permethrin (3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate
Source:	Zeneca Agrochemicals
Purity:	99.4%
cis/trans:	44.6/55.4
Description:	White powder

Labelled Material:

Chemical:	[^{14}C]-cyclopropyl-labelled permethrin, cis/trans isomeric ratio 44.6:55.4
Specific activity:	2.093 Gbq/mmol
Radiochemical purity:	>99%

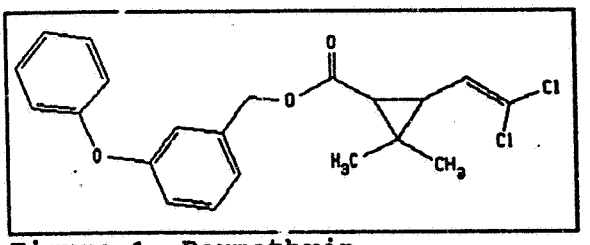

Figure 1 Permethrin

Test System:

Species	Rat - males only.
Strain:	Wistar derived Alpk:Apfsd
Supplier:	Barriered Animal Breeding Unit of Alderley Park
Age:	5-9 weeks on arrival
Diet:	Pelleted Porton Combined Diet

Basic Experimental Design:

In this study 4 groups of 24 male rats were prepared

and dosed as follows:

Group[1]	Treatment	Dose mg permethrin/rat	Sacrifice times (hrs)[3]
Group 1	Formulation Concentrate	9.1	0.5, 1, 2, 4, 10 and 24
Group 2	1/10 dilution[2]	0.86	"
Group 3	1/100 dilution	0.08	"
Group 4	1/1000 dilution	0.004	"

1. 24 rats per treatment level.
2. Formulation diluted with water.
3. There were four rats sacrificed per treatment group at each time interval.

Preparation: The backs and shoulders of the rats were shaved 24 hours before application of the dose. The rats without evidence of damaged skin were washed with acetone to remove sebum and rubber O rings (25.5 mm id 3 mm thick, two per rat) were glued to the skin, one behind each shoulder with cyano-acrylate glue. The internal area of the skin within each O ring was approximately 5 cm^2. A Queen Anne collar was secured to each rat.

Application of the dose. 20 ul of the test materials were applied to each space within the O rings (total area about 10 cm^2) to rats which were said to be inspected for undamaged O rings. Following application of the test material, the suspension was allowed to dry, and the application site was protected by applying cyano-acrylate glue around the surface of the O ring and superimposing a second O ring to which was glued a fine permeable nylon gauze. For the experiment with the 1/10 dilution, the O ring was covered with an "active carbon filter". This procedural difference is not considered by TB-I to compromise the study.

In determining the amount of radioactivity applied to each animal, the "moving average" of the amount of radiolabelled material recovered from the volumetric flask taken before and after each group of up to four rats, plus the radioactivity retained in each polyproplyene pipette tip used in sampling. This calculation was adjusted for the amount of material remaining in the pipettes. This procedure was used for all animals except for animals 11 and 12 because there was insufficient material in the flask. For these animals, the amount applied was calculated using only the sample taken preceding the dosing of these animals. Appendix D of the study report presents data on the amount of radioactivity (in Kbq) applied to each rat. Typically about 300 Kbq were applied to each rat.

Following dosing, the rats were refitted with the Queen Anne Collars and returned to metabolism cages. At 0.5, 1, 2, 4, 10 and 24 hours after application of the test material, the rats were anesthetized with Fluothane vapor, exsanguinated by cardiac puncture and blood samples collected. Prior to cardiac puncture, the O rings and coverings were removed and the area washed with 3% aqueous solution of Teepol-L with sponge swabs, all rinses and swabs were saved. Following sacrifice, an area of the skin encompassing the application site was removed and attached to a cork block. The stratum corneum of this skin was removed by means of stripping with adhesive tape. The pieces of tape were then retained in a single container for analysis. The residual

skin was also retained for analysis. The bladder was exposed and the urine collected and added to the urine in the collection device of the metabolism cage. The carcass was saved separately (at -20°C). Urine and feces were collected and the cages were washed with water:ethanol (1:1). The study methods section outlines the methods used in radioactivity assessment of each sample. These procedures are attached. (Appendix II)

In summary, the following samples were assessed for each animal:

skin wash	protective cover
stratum corneum	residual skin (at application site)
untreated skin	urine
feces	cage wash
carcass	blood

Statistics. The sample means and standard deviations were calculated. No group comparative statistics were determined.

Results

There were no reactions to treatment with permethrin reported. All dosed animals survived.

1. Total recovery. The mean percent of the total dose recovered together with the range for each dose level are listed in Table 1 below:

Table 1. Total recovery of labelled permethrin at each dose level.

Dose Level	Mean Percent Recovery[1]	Range
9.1 mg permethrin/rat	95.86 ± 2.01	(98.09 to 92.68)
0.86 mg permethrin/rat	96.99 ± 1.49	(98.56 to 94.33)
0.08 mg permethrin/rat	99.77 ± 3.53	(106.58 to 97.29)
0.0004 mg permethrin/rat	98.11 ± 2.59	(101.50 to 94.69

Data are from Tables 2, 4, 6 and 8 of the study report.
1. The mean is the mean of the percent recovery for the six individual times the rats were sacrificed and assessed.

The mean recovery being greater than 95% indicates good study efficiency. In general the time of sacrifice did not influence the amount recovered although the lowest recovery (92.68%) was in the 24 hour sacrifice for the highest dose of treatment.

2. Table 2 illustrates the dose and time relationship between the percentage recovered that was considered absorbable (in corneum, residual skin and untreated skin), systemically absorbed (in urine, feces, cage wash and carcass) and the potential total (absorbable plus absorbed). Table 2 also illustrates the amount

recovered in the wash and cover and the total recovery. These three data sets are discussed as follows.

Table 2. Dose and time relationship for absorbable and absorbed permethrin.

Hours	Absorbable Corneum	Absorbable Residual skin	Absorbed[1]	Total[2]	Wash/cover[4]	Total Recovered
Formulation Concentrate (9.1 mg permethrin/rat) [From Table 2]						
0.5	2.01	(0.48+0.21)[3]	0.16	2.86	95.24	98.09
1.0	1.70	(0.49+0.30)	0.18	2.67	94.56	97.22
2.0	2.63	(0.84+1.29)	0.60	5.36	91.81	97.18
4.0	1.93	(1.04+1.10)	1.18	5.25	89.83	94.89
10.0	1.78	(1.02+0.67)	1.26	4.73	90.16	94.89
24.0	3.66	(1.39+0.27)	3.71	9.03	83.65	92.68
1/10 dilution (0.86 mg permethrin/rat) [From Table 4]						
0.5	10.42	(1.20+0.65)	0.57	12.84	84.09	96.92
1.0	11.32	(1.22+0.61)	0.41	13.56	84.59	98.14
2.0	11.36	(1.41+0.16)	0.32	13.25	85.31	98.56
4.0	14.51	(2.66+0.17)	0.90	18.24	78.48	96.71
10.0	12.97	(2.45+0.24)	2.45	18.11	79.16	97.28
24.0	10.25	(3.13+0.35)	8.60	22.23	71.99	94.33
1/100 dilution (0.08 mg permethrin/rat [From Table 6]						
0.5	32.84	(2.43+0.31)	0.25	35.83	61.47	97.29
1.0	30.33	(3.26+0.88)	0.50	34.97	64.91	99.86
2.0	36.28	(1.77+0.60)	0.66	39.31	67.27	106.58
4.0	29.46	(2.40+0.44)	1.29	33.59	66.24	99.84
10.0	25.25	(3.11+0.45)	3.57	32.38	65.16	97.54
24.0	31.40	(2.80+0.30)	10.06	44.56	52.98	97.55
1/1000 dilution (0.004 mg permethrin/rat [From Table 8]						
0.5	18.36	(0.83+0.17)	2.47	21.83	79.67	101.50
1.0	17.33	(0.87+0.15)	2.08	20.43	79.39	99.82
2.0	14.24	(2.20+0.19)	2.03	18.66	79.10	97.74
4.0	22.22	(2.87+0.16)	2.25	27.50	71.74	99.24
10.0	14.61	(3.06+0.26)	4.16	22.09	72.60	94.69
24.0	14.92	(3.37+0.66)	11.12	30.07	65.58	95.65

1. Absorbed is total of urine, feces cage wash and carcass.
2. Total absorbed and absorbable.
3. Residual skin includes the residual application site and the untreated skin.
4. The "wash/cover" data are for the amount recovered in the wash and covering and is unabsorbable.

Systemically absorbed permethrin. The percentage of the dose actually systemically absorbed varies from as low as 0.16% (compare 0.5 hours for the undiluted material) to as high as 11.12% (compare the 1/1000 dilution at 24 hours). **The maximum percentage of permethrin actually systemically absorbed is 11.12%.**

Systemically absorbed permethrin is progressive with time but this is obscured at the interval 0.5 to 4 hours for the 1/1000 dilution.

Systemically absorbed permethrin was lowest for the undiluted material but the three diluted preparations had similar (8.6%, 10.06% and 11.12%) absorption rates at 24 hours. At lower time intervals, there was a lower percentage absorbed but probably only for the lowest dose was this difference meaningful.

Absorbable permethrin. Most of the absorbable permethrin adheres to the stratum corneum (1% to 37%) with lesser amounts being recovered in the residual skin (0.48% to 3.37%) and untreated skin (0.15% to 1.29%). The percentage of permethrin on the corneum was not linear with time. The percentage of permethrin in the residual skin showed some time dependence but not always. As the amount of permethrin decreased, the percentage absorbable increased but only to the 1/100 dilution. The 1/1000 dilution actually had less adhering to the skin.

Total absorbed and absorbable permethrin. Time dependence was obvious for the undiluted material but less obvious for the diluted preparations. The total percentage of absorbable and absorbed permethrin varies from 2.67% to 44.56% with the maximum percentage being for the 1/100 dilution at 24 hours.

Aside from the radioactivity in the skin, after 24 hours the largest fraction of radioactivity was found in the carcass with there being means of 2.64%, 5.49%, 6.29% and 7.08% in the carcass for the 9.1, 0.86, 0.08 and 0.004 mg permethrin/rat dose groups. The urine (2.45%), feces (1.17%) and cage washings (0.42%) made up the balance of the absorbed material (percentages given for the 0.004 mg permethrin/rat group, see also Table 8 attached)*. Blood levels were very low (refer to Table 9 from the study report attached) but reached a maximum of 0.382 ± 0.110 for whole blood and 0.754 ± 0.251 ug equivalents of permethrin/g plasma for the 24 hour 9.1 mg permethrin/rat dose group.

CONCLUSIONS/DISCUSSION. This study is classified as ACCEPTABLE and satisfies the requirement for a series 85-2 dermal penetration study with the product 2EC formulation. These data can be used to support the registration of permethrin 2EC formulation and similar formulations. Additional series 85-2 dermal penetration studies with permethrin may be required to support other formulations of permethrin on a case by case basis.

* Appendix III

Appendix I

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Selection of A Dermal Penetration Factor

Based on this study, numerous dermal penetration factors can be selected based on Table 2 above depending on the duration of exposure, the amount of permethrin exposed to and whether or not the amount adhering to the skin should be included in the risk assessment. Based on the pattern of the factors, the following simplified values are considered to be appropriate for use in risk assessment:

Exposures ≤ 0.32 mg/kg*, 45%.

Exposures > 0.32 mg/kg, 22%.

These percentages are generally appropriate for all time intervals.

[*0.32 mg/kg corresponds to the dose level of 0.08 mg permethrin per rat when it is assumed that the rats had an average weight of 250 gm.]

Note: The factor of 45% is the closest percentage to 44.56% for the 24 hour 0.08 mg permethrin/rat group and the 22% is the closest percentage to the 22.33% for the 24 hour 0.86 mg permethrin/rat group dose group. These factors are based on 24 hours of exposure, TB-I recognizes that exposure for periods of less than 24 hours would result in less absorption, but there is no control over the length of time a person would be exposed to permethrin. Good personal hygiene would probably result in a person removing the permethrin within a few hours of exposure. Such activity would still result in 32-39% of the 0.08 mg permethrin/rat (0.32 mg/kg) being absorbed. Thus, TB-I considers the factor of 45% is appropriate for exposure to permethrin of ≤ 0.32 mg/kg.

TB-I notes that there was a general progression of increased permethrin absorption up to 24 hours without an indication of a plateau. Thus, exposure to permethrin for periods of longer than 24 hours may result in a higher percentage of the exposed dose being absorbed. TB-I, however, considers that practice of good hygiene would result in very few exposures of greater than 24 hour .

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Page 1 is not included in this copy.

Pages 13 through 16 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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[81-6. Maximization test/permethrin/1989]

Reviewed by: John Doherty, Ph.D., D.A.B.T.
Section IV, Toxicology Branch I (7509C)
Secondary reviewer: Marion Copley, DVM.
Section IV, Toxicology Branch I (7509C)

6/5/95

6/5/95

DATA EVALUATION REPORT

STUDY TYPE: 81-6. Dermal sensitization study - guinea pig maximization test.

MRID NO.: 410311-06 **TOX. CHEM. NO.:** 652BB
PC No.: 109701

TEST MATERIAL: Technical permethrin, 95/6% purity.

STUDY NUMBER: CTL/P/2456

SPONSOR: ICI Agrochemicals

TESTING FACILITY: ICI Central Toxicology Laboratory, Cheshire, UK.

TITLE OF REPORT: "Permethrin: Skin Sensitization Study"

AUTHOR: A.M. Leah

REPORT ISSUED: February 21, 1989
[In-life phase: November and December 1988]

EXECUTIVE SUMMARY:

A group of 20 female guinea pigs (Dunkin Hartley) were inducted intradermally with 10% permethrin in corn oil and both neat and 30% solution of permethrin and later challenged with neat and 30% permethrin solutions in a guinea pig maximization test. (MRID #410311-06).

9 of 20 total guinea pigs produced indications of a positive response when none of the 10 total guinea pigs had definite scores for reaction. **Permethrin was demonstrated to be a moderate dermal sensitizer in the guinea pig maximization test,** but a weight of evidence evaluation of other sensitization study data do not indicate that permethrin should be regulated as a potential sensitizer in humans.

Classification: ACCEPTABLE. The guinea pig maximization study is one of several types of dermal sensitization studies run with permethrin and is considered to have a high rate of false positives. Thus, the determination that permethrin causes dermal sensitization should be based on the weight of the evidence for all sensitization studies and use history of the chemical. Other studies including some with humans do not indicate that permethrin should be regarded as a potential dermal sensitizer in humans.

[81-6. Maximization test/permethrin/1989]

Quality Assurance Statement: Provided.
Good Laboratory Practice Statement: Provided.
Statement of Data Confidentiality Claims: No claim of confidentiality indicated.
Flagging Statement: Provided.

REVIEW

Experimental Constants:

Test Chemical:

Chemical:	Technical permethrin
Purity:	95.6% (as per certificate of analysis RS/38/F)
Reference:	P56
CTL Ref #:	Y00040/085/001
Description:	Brown liquid

Positive Control:

Chemical:	Formaldehyde (40% in water).

Test System:

Species/strain:	Guinea pigs-albino Alpk:Dunkin Hartley - females only.
Supplier:	Animal Breeding Units, ICI Pharmaceutical Cheshire, England.
Weight:	234-299 for main study, 262-385 for positive control study.
Housing:	Individually.
Diet:	Labsure RGP Guinea Pig Diet.

Basic Experimental Design:

This study was based on the maximization test of Magnusson and Kligman. In the main study, two groups of female guinea pigs consisting of 10 controls and 20 dosed with permethrin (10% w/v in corn oil for the intradermal induction phase, undiluted permethrin for the topical induction and challenge phases).

The test dose of permethrin was determined on the basis of a preliminary dose range finding study in which sets of two or more guinea pigs were assessed for their reaction to intradermal, topical applications at either induction or challenge

Induction. The induction phase consisted of removing the hair for the scapular region and a row of three injections (0.05-0.1 ml each) was made on each side of the mid-line. These injections were:

i. Top: Freund's Complete Adjuvant plus corn oil (1:1).
ii. Middle: Test sample in corn oil.
iii. Bottom: Freund's Complete Adjuvant plus test sample in corn oil (1:1) preparation .

One week later the scapular region was clipped again and treated with undiluted test samples (0.2-0.3 ml) applied on a

filter paper which was held in place by a piece of surgical tape for 48 hours.

Controls were treated similarly except that the bottom row was treated the same as the top row and the topical applications consisted of corn oil only.

Challenge. The challenge was made two weeks after the topical inductions. The pigs were prepared by having their hair again clipped and an occlusive dressing applied which consisted of two pieces of filter paper stitched to a piece of rubber sheeting. Undiluted test sample (0.05-0.1 ml was applied to one of the pieces of filter paper and a 30% (w/v) preparation in corn oil (0.05-0.1 ml) was applied to the second piece of filter paper. The dressing was placed on the guinea pig so that the undiluted test sample was on the left shorn flank and the 30% preparation was on the right short flank. The filter papers were then covered with adhesive bandage which was secured by adhesive PVC tape. The test material was kept in contact for 24 hours before removal. The position of the papers on the skin was identified using a black waterproof marker-pen. The guinea pigs were assessed for reactions after 24 and 48 hours following removal of the challenge dose.

Positive control. Formaldehyde as a 0.3% dilution in deionized water was used for the intradermal injections and a 30% (w/v) dilution was used for the topical induction and challenge applications.

Results

One test and one control animal died from causes reported to be unrelated to treatment although the cause of death or the conditions of morbidity were not described. Three animals were eliminated from further analysis: two permethrin treated animals and one control. The bandage was reported to have slipped form the control animal and the two permethrin treated guinea pigs were reported to have an "equivocal response" No explanation or description was provided for the "equivocal response".

The formaldehyde positive control treated guinea pigs were reported to have developed scattered mild to intense redness and swelling in all test animals with scores ranging from 1 to the maximum score of 3. The reaction to formaldehyde was described as extreme.

None of the 9 guinea pigs had reactions to challenge treatment with neat permethrin at either 24 or 48 hours. One guinea pig challenged with 30% permethrin had a score of 1 that was also classified as doubtful at 24 hours but the score for this animal was 0 at 48 hours.

The study report asserts that 9 of 19[1] guinea pigs challenged with permethrin developed redness that was scattered mild or moderate diffuse. Thus the study indicated that permethrin is a moderate skin sensitizer using the guinea pig maximization test. Table 1 (photocopied from the study report, attached) illustrates the results of the challenge doses with permethrin, It is noted, however, that although the text of the study report states that as many as three animals were not included in the assessment these animals are not indicated in this table or elsewhere in the study report.

Ten guinea pigs dosed with neat permethrin had scores of 0 for both time intervals. Five guinea pigs had a score of 1 at 24 hours only. Three had a score of 1 at both 24 and 48 hours. One guinea pig had a score of 2 at 24 hours and 1 at 48 hours.

DISCUSSION/CONCLUSION. This study is classified as ACCEPTABLE and to demonstrate that permethrin is a moderate sensitizer in the guinea pig maximization test. TB-I notes discrepancies in the study report with regard to the reporting of the animals for which were included in the analysis. The report results section of the report states that as many as three were not included, but the summary table attached reports results for all 20 animals in the test group without indicating which guinea pigs were not included in the assessment. Although, TB-I recognizes this discrepancy, providing and identifying the exact number of animals included in the assessment by the study author will not change the conclusions of the study that permethrin is a moderate sensitizer in the guinea pig maximization test.

The significance of the positive finding in this guinea pig maximization study does not require that permethrin be regarded a sensitizer to humans. This type of study which utilizes Freund's adjuvant tends to have a high rate of false positives. Thus, the actual determination that permethrin is a potential dermal sensitizer to humans should be made on a weight of evidence assessment of available data that includes all other series 81-6 sensitization studies and product incident history for products containing permethrin.

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[1]The exact number of permethrin treated animals that were included in the assessment is not clear from reading the study report. In the results section, three guinea pigs are said to be omitted from the analysis, one with an equivocal response, one that died and one from which the bandage slipped. This would give nine with indications of permethrin reaction out of 17 animals or 53%.

Page 21 is not included in this copy.

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